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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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08/922,240 08/27/97 SCHREIBER

S APV-007.01

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BOSTON MA 02109

HM12/0424

EXAMINER

SORBELLO, E

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1633

DATE MAILED:

04/24/01

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

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|------------------------------|-----------------|------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 08/922,240 | SCHREIBER ET AL. |
| Examiner | Art Unit | |
| Eleanor Sorbello | 1633 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 15 February 2001.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-27,29-33,36 and 38-44 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) 32,33,36 and 44 is/are allowed.
- 6) Claim(s) 1-27,29-31 and 38-43 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) Notice of References Cited (PTO-892)
- 16) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 18) Interview Summary (PTO-413) Paper No(s) _____.
- 19) Notice of Informal Patent Application (PTO-152)
- 20) Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. Receipt is acknowledged of a request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e) and a submission, filed on 2/12/2001.

Response to amendment

2. Applicant's preliminary amendment and response to the official Office Action mailed 08/11, 2000 as Paper No. 14, has been received and filed on 2/15, 2001 as Paper No. 18C. Claims 1-2, 6-8, 16, 20-22, 26, 27, 31-33, 36 and 38 have been amended, and claims 40-44 have been added. Claims 1-27, 29-33, 36, 38-44 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1-27, 29-33, 36 and 38-39 stand rejected under 35 USC § 112, first paragraph for reasons of record. Applicant's amendments have been fully considered but they do not necessarily change the breadth of the claims and context of use.

The claims are directed to a method of inhibiting activation of T cells wherein T cell was engineered ex vivo to express a gene encoding any mutated MBP by contacting the cell with the corresponding macrolide. The claims are further directed to a method of inhibiting transcription of NFAT dependent genes in T cells by the engineering the T cells ex vivo to express a gene encoding any mutated MBP by contacting the cell with the corresponding macrolide. The claims further encompass

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methods of transplantation of the aforesaid engineered cells as a method for reducing graft-versus-host disease (GVHD).

As stated in the previous office action, in view of the breadth of the claims being drawn to the (a) inhibition of the activation of T cells by contacting the cells with any ~~mutated MBP~~, in the presence of the corresponding macrolide; and (b) in view of the claims drawn to ex-vivo gene therapy wherein GVHD is reduced by the administration of the aforementioned transfected cells in the presence of the corresponding macrolide; the specification is not enabled.

The claims however, are enabled for *in vitro* transfection of T cells engineered ex-vivo by MBP to express mutated MBP such as mutated cyclosporin, rapamycin and FK506 in the presence of the corresponding macrolide wherein NF-AT dependent genes in the T cells are inhibited.

The claims stand rejected for reasons of record due to the unpredictability in the art, the guidance provided, the breadth of the claims and undue experimentation required for one of skill in the art to make and use the instant invention as claimed.

5. Claims 40-43 (newly added) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 40-43 are directed to a method for selectively decreasing T cell activation utilizing a macrolide which is any analog of cyclosporin, FK506 or rapamycin together with the corresponding MBP. However all analogs of cyclosporin, rapamycin or FK506 have not been described in the specification. In the absence of such, it is not clear what specific analogs applicants are claiming, as the function of the macrolide is to bind the mutated form of MBP less than the wild type (by having a K_d less than the wild type) and therefore to decrease the T cell activation. In the absence of description of all analogs of cyclosporin, rapamycin or FK506, it is not clear that applicants have adequately described that which they are claiming.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the *invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only cyclosporin, rapamycin or FK506 but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

6. Claims 40-43 (newly added) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The claims are directed to a method of decreasing T cell activation by contacting T cells with the MBP which is the mutated form of FK506, cyclosporin, or rapamycin utilizing any analog of cyclosporin, rapamycin or FK506. However it is not clear that applicants are enabled for such by utilizing any and all analogs of cyclosporin, FK506 or rapamycin, but are enabled for only cyclosporin, FK506 or rapamycin. In the absence of such, it is not clear what specific analogs applicants are claiming. The claims are directed to methods for reducing the K_d , and since it is not clear what the binding constant will be unless the macrolide and the mutated form are brought in contact with each other, it is not clear if the goal of reducing the binding constant will be accomplished. It might very well act contrary to the intended goal.

Therefore, in view of the breadth of the claims, lack of guidance in the specification, lack of examples provided wherein only specified analogs of cyclosporin, FK506 or rapamycin have been used, and have had success in accomplishing the intended use of reducing the K_d value, one of skill in the art will require undue experimentation to make and use the invention as claimed.

Conclusion

7. Claims 32, 33, 36 and 44 are allowed.
8. Claims 1-27, 29-31 and 38-43 are rejected.
9. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Deborah Clark
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